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December 5, 2005

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2005P-0273, "Petition for mandatory calcium addition to current cereal-grain enrichment

Dear Sir/Madame,

Enclosed please find a copy of : CFSAN/Office of Nutritional Products, Labeling, and Dietary Supplements, October, 12 2005. Qualified Health Claims: Letter Regarding Calcium and Colon/Rectal, Breast, and Prostate Cancers and Recurrent Colon Polyps (Docket No. 2004Q-0097), Pages 1-30.

We request that this published document be added to our petition docket number 2005P-0273, since it includes relevant FDA conclusions to support the utility of additional dietary calcium in reducing the risk of colon/rectal polyps and colon rectal cancer. This is illustrated in the following quotation form Section VI, Conclusions:

"FDA concludes that there is sufficient evidence for qualified health claims about calcium and colon/rectal cancer and calcium and colon/rectal polyps, provided that the qualified claims are appropriately worded so as to not mislead consumers."

The authors of our petition believe that this conclusion of the FDA review for calcium dietary supplements, also bears directly on our petition to add modest calcium addition to cereal-grain enrichment, in accord with the Specific Aim No. 2 in our petition, which states:

"To broaden the range of commonly consumed foods as dietary sources of intakes of calcium, at very low cost, in order to achieve a generalized modest increase of calcium intake beyond the variability of dietary intake of the present major calcium dietary sources (e.g. milk, dairy products, some enriched fruit juices, dietary supplements, etc.) which are not generally consumed by the entire population."

Labeling requirements should pose few problems in adaptation to cereal-grain products.

Sincerely,

Harold L. Newmark

Harold L. Newmark, D.Sci. (Hon.)

HLN:ff

cc: R. Heaney
P. Lachance

2005P-0273 SUP 1

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

CFSAN/Office of Nutritional Products, Labeling, and Dietary Supplements
October 12, 2005

Qualified Health Claims: Letter Regarding Calcium and Colon/Rectal, Breast, and Prostate Cancers and Recurrent Colon Polyps

(Docket No. 2004Q-0097)

Jonathan W. Emord, Esq.
1800 Alexander Bell Drive,
Suite 200
Reston, Virginia 20191

RE: Health Claim Petition - Calcium and colon/rectal, breast, and prostate cancers and recurrent colon polyps (Docket No. 2004Q-0097)

Dear Mr. Emord:

This letter responds to the health claim petition dated October 9, 2003, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Marine Bio USA, Inc. pursuant to Section 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(5)(D)). The petition requested that the agency authorize several health claims characterizing the relationship between the consumption of calcium and a reduced risk of various cancers and/or health-related conditions.

The petition proposed as model health claims for dietary supplements the following claims:

1. Calcium may reduce the risk of colorectal cancer.
2. Calcium may reduce the risk of colon cancer.
3. Calcium may reduce the risk of rectal cancer.
4. Calcium may reduce the risk of breast cancer.
5. Calcium may reduce the risk of prostate cancer.
6. Calcium may reduce the risk of colorectal, colon, rectal, breast, and prostate cancers.
7. Calcium may reduce the risk of breast and prostate cancers.
8. Calcium may reduce the risk of colorectal, colon, and rectal cancers.
9. Calcium may have anticarcinogenic effects in the colon, breast and prostate.
10. Calcium may reduce the risk of recurrent colon polyps.

FDA informed you, on October 24, 2003, that FDA was not able to acknowledge receipt of the petition and begin its preliminary review of the petition because the petition was not complete. In response, you supplied the needed information in supplemental submissions received by FDA on November 25 and December 4, 2003. FDA acknowledged the petition in a letter dated December 9, 2003, which initiated FDA's preliminary review of the petition. In that letter, FDA also informed you that the date by which FDA would either file or deny the petition was March 4, 2004.

Based on a preliminary review, FDA determined that the scientific evidence supporting the proposed health claims does not meet the "significant scientific agreement" standard in 21 CFR 101.14(c) which is applicable to dietary supplements. FDA notified you of this decision and you submitted a letter dated March 2, 2004, stating that your client, Marine Bio USA, Inc., chose to seek FDA review of the petition as a qualified health claim. Accordingly, FDA filed the petition on March 16, 2004, as a qualified health claim petition and posted the petition on the FDA website for a 60-day comment period, consistent with the agency's guidance for procedures on qualified health claims[1]. In a letter dated June 16, 2004, you notified FDA that Marine Bio Co. Ltd. is now the petitioner of record for this petition, originally submitted by its wholly owned subsidiary, Marine Bio USA, Inc. The initial deadline for FDA's response on the petition was October 27, 2004. After mutual agreement, the deadline for the agency's response was last extended to October 12, 2005.

The agency received a total of two comments on this petition, one from industry (Wyeth Consumer Healthcare) and one from academia (Harvard Medical School). The comment from industry concerned the claims for calcium and colorectal cancer and recurrent colon polyps and supported a claim similar to one found in the petition (i.e., "Calcium may reduce the risk of colon polyps"). This comment also requested that FDA allow the following modified version of the claim: "Calcium may reduce the risk of recurrent colon polyps, a major risk factor for colon cancer." The comment from academia concerned the claims for calcium and prostate cancer and stated that the evidence presented to support a benefit of calcium on prostate cancer risk was mischaracterized and that, far from making the case for a protective effect of calcium on prostate cancer risk, the evidence strongly suggests that calcium increases the risk of prostate cancer. For example, of the 29 studies reviewed in the comment, 17 found that calcium or milk significantly increased the risk of prostate cancer, 4 found a trend that calcium or milk is associated with prostate cancer, and only one study found that calcium reduced the risk of prostate cancer. The comment concluded that it is premature to conclude that there is a causal association between calcium and prostate cancer, and, if anything, the data suggest the need for careful further study of the potential downside of increased calcium intake in men instead of encouraging greater calcium intake. FDA considered the relevant comments in its evaluation of the petition.

This letter sets forth the results of FDA's scientific review of the evidence for the proposed claims related to consumption of calcium and reduced risk of certain cancers, including the basis of FDA's determination that the current scientific evidence for the proposed health claims is appropriate for consideration of qualified health claims for calcium and reduced risk of colon/rectal cancer and colon/rectal polyps. This letter also provides the factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims for dietary supplements with respect to consumption of calcium and a reduced risk of colon/rectal cancer and colon/rectal polyps.

Finally, the letter sets forth the basis for FDA's determination that there is no credible scientific evidence to support qualified health claims for calcium and reduced risk of breast cancer and prostate cancer.

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.[2] In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.[3] FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[4]

The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[5]

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,[6] review articles,[7] and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease or health-related condition, or both, but can not by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[8] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine, National Academies of

Science, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors such as a control group or a statistical analysis means that scientific conclusions cannot be drawn from the study (Spilker et al., 1991, Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects --e.g., age, smoker vs. non-smoker was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[9] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated[10], and the overall consistency[11] of the total body of evidence.[12] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified calcium as the substance for the proposed claims. Calcium, one of the essential nutrients for humans, is a component of milk and milk products (approximately 300 mg per serving) and other food sources (e.g., Chinese cabbage, kale, and broccoli) (Institutes of Medicine, 1997). Thus, the agency concludes that the substance, calcium, is a component of food and meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified colorectal cancer, rectal cancer, colon cancer, breast cancer, prostate cancer and colon/rectal polyps as the diseases or health-related conditions for the proposed claims.

Cancer is a constellation of more than 100 different diseases, each of which is characterized by the uncontrolled growth and spread of abnormal cells (American Cancer Society, 2004). Cancers at different organ sites have different risk factors, treatment modalities, and mortality risk (American Cancer Society, 2004). Both genetic and environmental risk factors may affect the risk of different types of cancers. Risk factors may include a family history of a specific type of cancer, cigarette smoking, alcohol consumption, overweight and obesity, exposure to ultraviolet or ionizing radiation, exposure to cancer-causing chemicals, and dietary factors. The etiology, risk factors, diagnosis, and treatment for each type of cancer are unique.[13] The agency concludes that colorectal cancer, colon cancer, rectal cancer, breast cancer, and prostate cancer are diseases and that colon/rectal polyps are health-related condition and thus, the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For dietary supplements, the applicable safety provisions require, among other things, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. 342(f)(1)(A))). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the Act (21 U.S.C. 342(f)(1)(D))).

The petition stated that calcium is an essential mineral that has a multitude of vital biological roles and also asserted that there is an absolute lack of any reports of clinically significant adverse reactions attributed to dietary calcium. Further, the petition stated that the final rule authorizing the health claim about calcium and osteoporosis concluded that calcium complies with the requirements of 21 CFR 101.14(b)(3)(ii). The petition stated that FDA has determined that ten calcium compounds have been demonstrated to be safe and lawful for use in dietary supplement. 58 FR at 2670 citing 56 FR at 60691. The petition also stated that calcium has prior sanctioned status as safe and lawful under the Act. Further, the petition noted that the North American Menopause Society, in its 2001 Consensus Opinion, stated that the side effect profile from recommended levels of calcium intake is insignificant and that no serious side effects are associated with those levels, and that the Physicians' Desk Reference (PDR) reported that calcium supplements are generally well tolerated.

In the final rule for the authorized health claim about calcium and osteoporosis (21 CFR 101.72) (58 FR 2665 at 2670; January 6, 1993), FDA identified ten specific calcium compounds [14] that are deemed to be safe and lawful for use in dietary supplements or as nutrient supplement (i.e., added to food) that may bear the calcium/osteoporosis health claim. These calcium compounds were either approved as food additives (21 CFR 172), generally recognized as safe (GRAS) substances (21 CFR 182), or affirmed as GRAS substances (21 CFR 184). All ten were approved, recognized, or affirmed as safe for use in a dietary supplement or as a nutrient supplement. Although the petition asserted that calcium has prior-sanctioned status as safe and lawful under the Act, there are no food ingredients that have prior-sanctioned status for nutrition supplement purposes (21 CFR 181).

At the time FDA published the final rule authorizing the health claim about calcium and osteoporosis (January 6, 1993), ingredients used in dietary supplements were subject to the premarket safety evaluations required for new food ingredients and for new uses of food ingredients. That is, such ingredients were required to be approved as food additives, determined as GRAS substances, or affirmed as GRAS substances before they could be used in food, including dietary supplements. With passage of the Dietary Supplement Health and Education Act in 1994 (DSHEA) (Pub. L. 103-417), Congress amended the Act to provide that ingredients for dietary supplements are exempt from premarket safety evaluations for food additives or GRAS substances. Instead, Congress provided that dietary ingredients are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. 342) (excluding the food additive adulteration provision), and, if applicable, the new dietary ingredient provisions in section 413 of the Act (21 U.S.C. 350b), which pertain to dietary ingredients that were not marketed in the United States before October 15, 1994.

Although calcium is known to be an essential nutrient, it can also cause adverse effects. The Institute of Medicine (IOM) of the National Academy of Sciences (Institute of Medicine, 1997) noted that the adverse effects of excess calcium intake in humans concerns calcium intake from "nutrient supplements" and that the most widely studied and biologically important possible adverse effects of excessive calcium intake are kidney stone formation, the syndrome of hypercalcemia and renal insufficiency (milk alkali syndrome), and the interaction of calcium with the absorption of other essential minerals. Using milk alkali syndrome as the clinically defined critical endpoint, the IOM identified the lowest-observed-adverse-effect level (LOAEL) of calcium intake in the range of 4,000 to 5,000 mg/day. The IOM established 2,500 mg of calcium as the tolerable upper intake levels (UL) for individuals over 12 months old by dividing a LOAEL of 5,000 mg by an uncertainty factor of 2 to take into account the relatively high

prevalence of renal stones in the U.S. population (12 percent) and potential increased risk of hypercalciuria and depletion of other minerals among susceptible individuals. The IOM defined the UL as the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population (Institute of Medicine, 1997).

Calcium is often contained in multiple vitamin and mineral dietary supplement products. Most of these products contain about 100 to 200 mg of calcium per reference amount customarily consumed (RACC) and recommend consumption of the dietary supplement once per day. Alternatively, calcium is also often contained in calcium only or calcium and vitamin D dietary supplement products to the exclusion of other dietary ingredients. These types of dietary supplements contain larger amounts of calcium than the multiple vitamin and mineral supplements, about 500 to 800 mg of calcium per RACC. The RACC for dietary supplements is the maximum amount recommended, as appropriate, on the label for consumption per eating occasion, or in the absence of recommendations, one unit, e.g., one tablet, capsule, packet, teaspoonful, etc. (see Table 2 of 21 CFR 101.12(b)). The maximum daily intake level of calcium from calcium only or calcium and vitamin D dietary supplements suggested in these products generally varies between 1,000 and 1,600 mg/day. The most recent nationally representative data, 1999-2000 National Health and Nutrition Examination Survey found the median calcium intake from foods, excluding dietary supplements, to be 735 mg/day for all individuals, excluding nursing infants and children (Ervin, 2004). Therefore, FDA believes that the combined amount of calcium from diet and dietary supplements would likely be kept within 2,500 mg/day.

FDA concludes at this time, under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), that the use of calcium in dietary supplements at levels necessary to justify the qualified health claims described in section IV is safe and lawful under the applicable provisions of the Act.

II. The Agency's Consideration of a Qualified Health Claim

FDA has identified the following markers to use in identifying risk reduction for purposes of a health claim evaluation involving cancer: incident cases of the particular cancer being studied (i.e., colon/rectal, breast, or prostate), and recurrent colon/rectal polyps for colon/rectal cancer. Colon/rectal polyp recurrence has been used as a surrogate marker for colon/rectal cancer and has been used by the National Cancer Institute as a surrogate marker for colon cancer prevention (Schatzkin et al., 1994). To evaluate the potential effects of calcium consumption on cancer risk, FDA considered these markers as indicators or predictors of disease.

The petition cited 542 publications as evidence to substantiate the relationship for this claim. These publications consisted of: 36 articles on the bioavailability, transport, or absorption of calcium; 113 review articles; 6 reports from Federal Register, Institute of Medicine, or the National Cancer Society; 2 chapters from text books; 1 abstract; 50 *in vitro* articles; 111 animal articles; 1 article that was not sufficiently translated; 75 research articles that did not address a relationship between calcium and cancer; 50 intervention studies on colon/rectal cancer and calcium; 76 epidemiological studies on colon/rectal cancer and calcium intake; 13 epidemiological studies for prostate cancer and calcium intake; and 8 epidemiological studies on breast cancer and calcium intake.

In addition to the studies included in the petition, FDA found two additional articles from a

literature search that evaluated calcium and colorectal cancer (Flood et al., 2005) and prostate cancer (Baron et al., 2005).

Below, FDA evaluated all of the available scientific information identified in relation to the proposed claims.

A. Assessment of Review Articles, Meta-Analyses, Book Chapters and Abstracts

Although useful for background information, the review articles, meta-analysis, book chapters, and abstracts do not contain sufficient information on the individual studies which they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement). Similarly, the lack of detailed information on studies summarized in review articles, book chapters, and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles, book chapters, and abstract supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationships claimed by the petitioner.

B. Assessment of Animal and *In Vitro* Studies

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease, and they can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the animal or *in vitro* studies submitted with the petition as providing any supportive information about the substance/disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of any type of cancer, nor can the studies mimic the human body's response to the consumption of calcium. Therefore, FDA cannot draw any scientific conclusions from the animal or *in vitro* studies regarding calcium and the reduction of risk of any type of cancer.

C. Assessment of Intervention Studies

Colon/Rectal Cancer or Polyps

The majority of published research did not differentiate between colon and rectal cancers, therefore the agency evaluated colon and rectal cancer together in this review. FDA identified a total of 50 intervention studies for its evaluation of a relationship between calcium intake and colon/rectal cancer. Of these 50 intervention studies, 48 did not provide information from which scientific conclusions could be drawn regarding the substance/disease relationship for one or more of the following reasons discussed below (see Appendix 1).

In two studies, the subjects had already been diagnosed with colon/rectal cancer. Because the subjects were already diagnosed with colon/rectal cancer, it was not possible to determine

whether calcium consumption reduced the risk of developing the cancer. Health claims characterize the relationship between a substance and a reduction in risk of contracting a particular disease.[15] Accordingly, these claims are necessarily about reducing the risk of a disease in people who do not already have the disease that is the subject of the claim. As a result, FDA considers evidence from studies in individuals already diagnosed with colon/rectal cancer only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. Given that such evidence is not available, the agency cannot draw any scientific conclusions from these two studies about consumption of calcium and reduced risk of colon/rectal cancer.

Thirty eight studies did not measure a validated surrogate endpoint of cancer (i.e. colon/rectal cancer incidence or colon/rectal polyp recurrence). Instead, the studies measured factors such as the fatty acid, bile acid or water content of feces, ornithine decarboxylase activity, or colon/rectal cell proliferation, which are not validated surrogate endpoints of colon/rectal cancer. Because these studies did not measure a validated surrogate endpoint, scientific conclusions about the relationship between calcium intake and a reduced risk of colon/rectal cancer could not be drawn from these studies.

Seven intervention studies provided supplemental calcium in combination with other vitamins that may affect colon/rectal polyp recurrence (selenium, vitamin E, vitamin C and β-carotene) or the studies used dairy products as the intervention substance, and were not controlled. Unless the test diet is controlled, intervention studies that evaluate nutrient intake from foods or multi-nutrient supplements must estimate the levels of the nutrient consumed based on the amount and type of food consumed or multi-nutrients taken during the study. However, the nutrient content of foods can vary (e.g., due to demographics (soil composition), food processing/cooking procedures, or storage (duration, temperature)). The nutrient content of the multi-nutrient supplements may also vary. Thus, if the test diet is not controlled for the type and amount of foods consumed or the type and amount of multi-nutrients taken, the amount of the nutrient consumed based on reports of dietary consumption or multi-nutrient supplements taken may not be accurately ascertained. These studies were not controlled for these factors. Therefore, no scientific conclusions can be drawn from them about the relationship between calcium supplements and colon/rectal polyp recurrence or colon/rectal cancer.

In addition, foods and multi-nutrient dietary supplements contain not only calcium, but also other nutrients that may be associated with the metabolism of calcium or the pathogenesis of cancer, colon/rectal polyp recurrence or colon/rectal cancer. Because foods consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (Sempos et al., 1999). (See Willett, 1990; Willett, 1998; Sempos et. al, 1999 regarding the complexity of identifying the relationship between a specific nutrient within a food and a disease). Similar consideration would apply to multi-nutrient supplements. For intervention studies on foods or multi-nutrient supplements, it is not possible to accurately determine whether any observed effects of calcium on colon/rectal cancer or polyp risk are due to: 1) calcium alone; 2) interactions between calcium and other nutrients; 3) other nutrients acting alone or together; or, 4) for foods, decreased consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of calcium-rich foods unless the studies are controlled so that it can be determined that the effects are from calcium alone,

and it is known that there are no confounders. These studies were not controlled. Therefore, scientific conclusions cannot be drawn from these studies about the relationship between calcium supplements and colon/rectal cancer or polyp risk.

Three studies were a republication or reanalysis of a study already being used in evaluating the proposed claim, thus the studies provided no new scientific data to evaluate the proposed health claim.

The Duris et al. (1996) study did not conduct statistical analysis between the control and intervention group for colon/rectal polyp recurrence. Statistical analysis of the relationship is a critical factor because it provides the comparison between subjects consuming calcium supplements and those not consuming calcium supplements to determine whether there is a reduction in cancer risk. When statistics are not performed on the specific substance/disease relationship, it cannot be determined whether there is a difference between the two groups. As a result, because this study provided no information about whether calcium reduces the risk of colon/rectal cancer or colon/rectal polyp recurrence, no scientific conclusions could be drawn from it.

Lastly, two high quality intervention studies evaluated the relationship between calcium and reduced risk of colon/rectal cancer (Baron et al., 1999; Bonithon-Kopp et al., 2000). Baron et al. (1999) was a randomized double-blind intervention trial on 930 subjects with a recent history (previous three months) of colon/rectal polyps. The mean age of the subjects was 61 ± 9 years and 70% of the subjects were men. Of the 930 subjects that underwent randomization, 832 completed the study follow-up of two colonoscopies, at one and four years after enrollment. After a three month placebo run-in period, the subjects were randomized to receive 3 g/day of calcium carbonate (1.2 g/day of elemental calcium) or placebo until the completion of the study. The relative risk for developing a polyp between the first and second endoscopy was 0.81 with a 95% confidence interval (CI) 0.67-0.99.[16] This study reported that calcium supplementation significantly reduced the risk of polyp recurrence in the colon and rectum.

Boniton-Kopp et al. (1999) was a randomized double-blind intervention trial on 665 subjects with a recent history of colon/rectal polyps. There were three groups in the study, 218 subjects received calcium gluconolactate and carbonate daily (2 g/day elemental calcium), 226 received 3.5 g of fiber per day, and 221 received a placebo. Approximately 60% of the subjects were males and the average age for the intervention groups was approximately 59 years. Both the calcium and placebo groups had a similar number of subjects complete the study, 176 for calcium and 178 for placebo. The adjusted relative risk for calcium supplementation and polyp recurrence in this study was 0.66 with a 95% CI of 0.38-1.17. Calcium supplementation did not significantly affect colon/rectal polyp recurrence in this study.

Breast Cancer

No intervention studies were submitted by the petitioner relating calcium and breast cancer risk reduction. The agency could not identify any additional relevant studies from a literature search.

Prostate Cancer

One intervention study was found by the agency relating to calcium and prostate cancer risk

(Baron et al., 2005). The report was designed to specifically evaluate the effect of calcium on colon/rectal polyp recurrence. Prostate cancer incidence was a secondary endpoint of the study. Significantly, the study did not screen for prevalent cases of prostate cancer at the beginning of the study. Consequently, the results may be biased due to an uneven distribution of prevalent cases in the treatment versus the placebo group. Because uneven distribution of important patient or disease characteristics between groups may lead to mistaken interpretation (Spilker et al., 1991), scientific conclusions could not be drawn from this study about the relationship between calcium and reduced risk of prostate cancer.

D. Assessment of Observational Studies

Several observational studies specifically evaluated supplemental calcium intake and colon/rectal cancer or polyp risk reduction. However, many observational studies calculated calcium intake from the diet or water.

The proposed claim is for a relationship between calcium dietary supplements and a reduced risk of colon/rectal, breast and prostate cancer, and recurrent colon/rectal polyps. In observational studies that calculate nutrient intake from conventional food, measures of calcium intake are based on recorded dietary intake methods such as food frequency questionnaires, diet recalls, or diet records, in which the type and amount of foods consumed are estimated. A common weakness of observational studies is the limited ability to ascertain the actual food or nutrient intake for the population studied. Furthermore, the nutrient content of foods can vary (e.g., due to demographics (soil composition), food processing/cooking procedures, or storage (duration, temperature)). Thus, it is difficult to ascertain an accurate amount of the nutrient consumed based on reports of dietary intake of foods.

In addition, conventional foods contain not only calcium, but also other nutrients that may be associated with the metabolism of calcium or the pathogenesis of colon/rectal, breast, or prostate cancer, and recurrent colon/rectal polyps. Because foods consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (Sempos et al., 1999). For instance, vitamin D regulates calcium absorption and metabolism and sodium and protein increases the urinary excretion of calcium (Institute of Medicine, 1997). See Sempos et. al. (1999), Willett (1990), and Willett (1998) regarding the complexity of identifying the relationship between a specific nutrient within a food and a disease). For studies based on recorded dietary intake of such foods, it is not possible to accurately determine whether any observed effects of calcium on kidney stone risk were due to: 1) calcium alone; 2) interactions between calcium and other nutrients; 3) other nutrients acting alone or together; or, 4) decreased consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of calcium-rich foods.

In fact, evidence demonstrates that in a number of instances, epidemiological studies based on the recorded dietary intake of conventional foods may indicate a benefit for a particular nutrient with respect to a disease but it is subsequently demonstrated in an intervention study that the nutrient-containing dietary supplement does not confer a benefit or actually *increases* risk of the disease (Lichtenstein and Russell, 2005). For example, previous epidemiological studies reported an association between fruits and vegetables high in beta-carotene and a reduced risk of lung cancer (Peto et al., 1981). However, subsequent intervention studies, the Alpha-Tocopherol and Beta Carotene Prevention Study (ATBC) and the Carotene and Retinol

Efficiency Trial (CARET), demonstrated that beta-carotene supplements increase the risk of lung cancer in smokers and asbestos-exposed workers, respectively (The Alpha-Tocopherol and Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996). These studies illustrate that the effect of a nutrient provided as a dietary supplement exhibits different health effects compared to when it is consumed among many other food components. Furthermore, these studies demonstrate the potential public health risk of relying on results from epidemiological studies, in which the effect of a nutrient is based on recorded dietary intake of conventional foods as the sole source for concluding that a relationship exists between a specific nutrient and disease risk; the effect could actually be harmful.

In *Pearson v. Shalala*, the D.C. Circuit noted that FDA had "logically determined" that the consumption of a dietary supplement containing antioxidants could not be scientifically proven to reduce the risk of cancer where the existing research had examined only foods containing antioxidants as the effect of those foods on reducing the risk of cancer may have resulted from other substances in those foods. 164 F.3d 650, 658 (D.C. Cir 1999). The D.C. Circuit, however, concluded that FDA's concern with granting antioxidant vitamins a qualified health claim could be accommodated by simply adding a prominent disclaimer noting that the evidence for such a claim was inconclusive given that the studies supporting the claim were based on foods containing other substances that might actually be responsible for reducing the risk of cancer. *Id.* The court noted that FDA did not assert that the dietary supplements at issue would "threaten consumer's health and safety." *Id.* at 656. There is, however, a more fundamental problem with allowing qualified health claims for nutrients in dietary supplements based solely on studies of foods containing those nutrients than the problem the D.C. Circuit held could be cured with a disclaimer. As noted above, even if the effect of the specific component of the food constituting the dietary supplement could be determined with certainty, recent scientific studies have shown that nutrients in food do not necessarily have the same beneficial effect when taken in the form of a dietary supplement. See Lichtenstein and Russell (2005). Indeed, not only have studies on single nutrient supplements established that the benefits associated with the dietary intake of certain nutrients do not materialize when the nutrients are taken as a supplement, but some of these studies have actually indicated an *increased* risk for the very disease the nutrients were predicted to prevent. *Id.* Thus, an observational study based on food provides no information from which scientific conclusions may be drawn for the single nutrient supplement.

Therefore, observational studies in foods do not provide any credible evidence for a claim for risk reduction for a single nutrient supplement because, in fact, the nutrient in supplement form may decrease, have no effect, or actually *increase* risk of the disease or health related condition. For the reasons set forth in Section V we have concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances because observational studies in food do not provide credible evidence of risk reduction for a single nutrient supplement.

Colon and Rectal Cancer

Of the 77 observational studies on colon/rectal cancer/polyps, 66 studies estimated calcium intake from either estimated dietary or water intake (see Appendix 1). Scientific conclusions could not be drawn from these studies regarding supplemental calcium and colon/rectal cancer risk because, for the reasons discussed above, food observational studies provide no information from which scientific conclusions can be drawn about a single nutrient supplement and a

reduced risk of a disease.

Six prospective cohort studies[17] evaluated the relationship between supplemental calcium and risk of colon/rectal cancer (Flood et al., 2005; Sellers et al., 1991; McCullough et al., 2003; Wu et al., 2002; Martinez et al., 2002; Hyman et al., 1998). All six studies were considered to be of high methodological quality.

The Flood et al. (2005) study followed a cohort of 45,354 women from the U.S. for approximately 8.5 years, identifying 482 cases of colon/rectal cancer during the follow-up. Calcium supplement consumption (>800mg/day) was associated with a decreased risk of colon/rectal cancer (relative risk of 0.76 and 95% CI of 0.56-0.98) (Flood et al., 2005). The Cancer Prevention Study II Nutrition cohort consisted of approximately 126,000 males and females from the U.S. who completed a detailed questionnaire regarding different lifestyle and dietary habits in 1992-1993 (McCullough et al., 2003). After four to five years of follow-up, 683 cases of colorectal cancer were identified in the cohort. Calcium supplement use was associated with a reduced risk of developing colon/rectal cancer with a relative risk of 0.69 and 95% CI of 0.49-0.96. However, when the cohort was stratified by gender, calcium supplementation had no significant effect on colon/rectal cancer incidence.

The Nurses Health Study and Health Professionals Follow-up study (87,988 females and 47,344 males, respectively) evaluated calcium intake and colon/rectal cancer risk over 10-16 years of follow-up, identifying 1,025 colon/rectal cancer cases (Wu et al., 2002). Current calcium supplement use was associated with a decreased risk of distal colon cancer incidence in a combined cohort analysis (relative risk of 0.69 and 95% CI of 0.51-0.94 compared to non-supplement users). When the cohorts were stratified by gender, calcium supplementation had no significant effect on distal colon cancer incidence. Calcium supplementation was not specifically evaluated in proximal colon cancer; however, total calcium intake (supplemental and dietary calcium combined) did not demonstrate any reduction in risk.

A cohort of 35,216 women from Iowa assessed calcium intake and colon cancer risk (Sellers et al., 1998). The women completed a questionnaire regarding dietary and supplemental sources of calcium in 1986 and were followed for 9 years with 241 colon cancer cases identified. Supplemental calcium use was associated with a significantly reduced risk of colon cancer incidence (relative risk of 0.6 and a 95% CI of 0.4-0.9) in women without a family history of colon cancer. There was no beneficial relationship between calcium supplementation and colon/rectal cancer in women with a family history of colon cancer.

Two prospective studies evaluated the association between calcium supplementation and polyp recurrence (Martinez et al., 2002; Hyman et al., 1998). Martinez et al. (2002) was a secondary analysis of an intervention study initially designed to evaluate fiber intake and polyp recurrence. The primary intervention had no effect on polyp recurrence. The study followed 1,304 males and females for three years. Calcium supplement use had no association with polyp recurrence (relative risk of 0.94 and 95% CI of 0.67-1.33). Hyman et al. (1998) performed a secondary analysis of an intervention trial designed to evaluate different anti-oxidant compounds (b-carotene, Vitamins C and E) and polyp recurrence. The intervention had no effect on polyp recurrence. The study followed 864 subjects for four years. Calcium supplement use had no association with polyp recurrence (relative risk of 0.76 and 95% CI of 0.42-1.38).

Five case-control studies[18] of moderate methodological quality evaluated the relationship between calcium supplement use and colon/rectal cancer risk (Marcus et al., 1998; White et al., 1997; Neugut et al., 1996; Whelan et al., 1999; Peleg et al., 1996). Marcus et al. (1998) conducted a case-control study in 678 controls and 512 female colon/rectal cancer cases from the United States. Supplemental calcium intake had no significant association with colon or rectal cancer risk (odds ratio of 1.0[19] and a 95% CI of 0.7-1.6 and odds ratio 0.8 with 95% CI of 0.5-1.6, respectively). White et al. (1997) found no significant association between calcium supplement use and colon cancer risk in 444 cases and 427 controls from the United States. Neugut et al. (1996) performed two different case-control studies in one publication; the first study compared 297 subjects newly diagnosed with polyps to 505 controls. There was no association between calcium supplement use and polyp occurrence (odds ratio of 0.9 and 95% CI of 0.2-4.0). The second case-control study contained 297 subjects with recurrent polyps and 347 controls (without recurrent polyps; but have a history of polyps). Calcium supplement use had no association with polyp recurrence (odds ratio of 2.9 and 95% CI of 0.6-9.5). Whelan et al. (1999) conducted a case-control study in 183 subjects diagnosed with recurrent colon/rectal polyp and 265 subjects without a recurrent colon/rectal polyps. Supplemental calcium intake was associated with a decreased risk of polyp recurrence (odds ratio of 0.51 and 95% CI of 0.27-0.96). Peleg et al. (1996) found no relationship between prescribed calcium supplement use and colon/rectal cancer risk in 93 colorectal carcinoma cases, 113 colorectal adenocarcinoma cases and 186 or 226 controls from the United States (odds ratio of 1.93 and 0.68 and 95% CI of 0.81-4.62 and 0.24-1.89).

Breast Cancer

FDA identified eight observational studies on dietary calcium and risk of breast cancer, consisting of two prospective cohort studies (Shin et al., 2002; Kneckt et al., 1996) and six case-control studies (Negri et al., 1996; Zaridze et al., 1991; Boyapati et al., 2003; Katsouyanni et al., 1988; Van 'T Veer et al, 1991; Graham et al, 1991). Seven studies measured calcium intake from estimated intake of foods (Kneckt et al.,1996; Zaridze et al., 1991; Boyapati et al., 2003; Katsouyanni et al., 1988; Van T' Veer et al., 1991; Negri et al., 1996; Graham et al., 1991; Kneckt et al., 1996). Scientific conclusions could not be drawn from these 7 studies about the relationship between supplemental calcium and breast cancer risk because, for the reasons discussed at the beginning of this section, food observational studies provide no information from which scientific conclusions can be drawn about a single nutrient and a reduced risk of a disease.

One study evaluated the relationship between calcium and breast cancer (Shin et al., 2002). This was a cohort study of high methodological quality that evaluated calcium supplement intake and breast cancer risk in 88,691 pre- and post-menopausal female nurses, with 3,482 cases identified during follow-up. Calcium supplement use was not significantly associated with breast cancer incidence in either group of nurses. Pre-menopausal women consuming greater than 900 mg/day of supplemental calcium had a relative risk of 1.10 and 95% confidence interval of 0.81-1.50 for developing breast cancer compared to women not consuming supplements. Postmenopausal women consuming greater than 900 mg/day of supplemental calcium had a relative risk of 0.93 and 95% CI of 0.81-1.08 for developing breast cancer compared to women not consuming calcium supplements. When supplemental calcium intake was stratified by dietary calcium intake, no significant association between supplemental calcium intake and breast cancer was found.

Prostate Cancer

FDA identified 13 observational studies on the relationship between calcium intake and prostate cancer. Ten studies estimated dietary calcium intake from food or water consumption (Chan et al., 2001; Chan et al., 2000; Schuurman et al., 1999; Berndt et al., 2002; Ohno et al., 1988; Hayes et al., 1999; Vlajinac et al., 1997; Chan et al., 1998; Tavini et al., 1999; Tzonou et al., 1999). Therefore, scientific conclusions could not be drawn from these ten studies about the relationship between supplemental calcium and prostate cancer risk because, for the reasons discussed at the beginning of this section, food observational studies provide no information from which scientific conclusions can be drawn about a single nutrient supplement and a reduced risk of a disease.

One prospective cohort study evaluated the relationship between calcium and prostate cancer and was of high methodological quality (Giovannucci et al., 1998). This study evaluated the effect of supplemental calcium use in a stratified analysis with dietary calcium intake. The cohort contained 47,781 males that were followed for eight years and 1,792 cases were identified. This study reported that the group consuming the least amount of dietary calcium (<600 mg/day) and the highest calcium supplement intake (>900 mg/day) was associated with a significant increase in the risk of metastatic prostate cancer (relative risk of 3.6 and 95% CI of 1.5-8.8). No stratified analysis of supplemental and dietary calcium use for total prostate cancer (metastatic and non metastatic prostate cancer) was evaluated. However, total calcium intake (supplemental and dietary combined) at the highest intake level (greater than 2 g/day) was significantly associated with an increased risk of prostate cancer.

In addition, two case-control studies of high methodological quality evaluated the relationship between supplemental calcium and prostate cancer risk (Kristal et al., 1999; Kristal et al., 2002). Kristal et al. (1999) was a case-control study that included 697 incident prostate cancer cases and 666 controls from the Seattle, Washington area. Calcium supplement use had no significant association with prostate cancer risk, even at the highest quartile of intake (odds ratio of 1.25 and 95% of 0.73-2.17). Kristal et al. (2002) was a case control study with 605 cases of cancer and 592 controls that evaluated calcium intake from supplements in a stratified analysis with dietary calcium intake. Calcium intake from supplements did not significantly affect prostate cancer risk.

Recurrent Colon/Rectal Polyps

Colon and rectal polyps were used in the above analysis of colon/rectal cancer since they are considered a surrogate endpoint for colon/rectal cancer. Because colon/rectal polyps are a health-related condition, independent from being a surrogate endpoint for colon/rectal cancer, they have been evaluated separately from colon/rectal cancer. Studies that measured the incidence of colon/rectal cancer are not relevant to the recurrence of colon/rectal polyps because colon/rectal polyps occur before the progression to colon/rectal cancer.

FDA identified 13 observational studies on calcium intake and colon/rectal polyps recurrence, consisting of two prospective cohort studies and 11 case-control studies. Nine case-control studies evaluated dietary calcium and colon/rectal polyp relationship (Benito et al., 1991; Boutron et al., 1996; Katschinski et al., 2001; Levine et al., 2001; Macquart-Moulin et al., 1987; Martinez et al., 1996; Martinez et al., 1997; Morimoto et al., 2002; Tseng et al., 1996). For the reasons discussed at the beginning of this section, scientific conclusions could not be drawn

from these nine studies about the relationship between supplemental calcium and colon/rectal polyps.

Two prospective cohorts evaluated the relationship between supplemental calcium and breast cancer (Martinez et al., 2002; Hyman et al., 1998). Both cohort studies were of high methodological quality. Martinez et al. (2002) was a secondary analysis of intervention studies initially designed to evaluate fiber intake and polyp recurrence. The primary intervention with fiber had no effect on polyp recurrence. The study followed 1,304 males and females for three years. Calcium supplement use had no association with polyp recurrence (relative risk of 0.94 and 95% CI of 0.67-1.33). Hyman et al. (1998) performed a secondary analysis of an intervention trial designed to evaluate different anti-oxidant compounds (β-carotene, Vitamins C and E) and polyp recurrence. The intervention had no effect on polyp recurrence. The study followed 864 subjects for four years. Calcium supplement use had no association with polyp recurrence (relative risk of 0.76 and 95% CI of 0.42-1.38).

Two case-control studies of moderate methodological quality evaluated the relationship between calcium supplement use and colon/rectal polyp risk (Neugut et al., 1996; Whelan et al., 1999). Neugut et al. (1996) performed two different case-control studies in one publication; the first study compared 297 subjects newly diagnosed with polyps to 505 controls. There was no association between calcium supplement use and polyp occurrence (odds ratio of 0.9 and 95% CI of 0.2-4.0). The second case-control study contained 297 subjects with recurrent polyps and 347 controls (without recurrent polyps, but have a history of polyps). Calcium supplement use had no association with polyp recurrence (odds ratio of 2.9 and 95% CI of 0.6-9.5). Whelan et al. (1999) conducted a case-control study in 183 subjects diagnosed with recurrent colon/rectal polyp and 265 subjects without a recurrent colon/rectal polyps. Supplemental calcium intake was associated with a decreased risk of polyp recurrence (odds ratio of 0.51 and 95% of 0.27-0.96).

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated[20], and the overall consistency[21] of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

Colon and Rectal Cancer

As discussed in Section II of this letter, there were two intervention studies and six prospective observational studies that provided information about the relationship between supplemental calcium intake calcium and colon/rectal cancer risk reduction. One intervention study reported a significant reduction in recurrent colon/rectal polyps after supplementation with 1.2 g/day of calcium (Baron et al., 1999). In contrast, the intervention study by Bonithon-Kopp et al. (2000)

reported no significant benefit of calcium supplementation. The Baron et al. (1999) study included more subjects and had a longer follow-up time than Bonithon-Kopp et al. (2000) which may have provided the study with more power (e.g., ability to detect a difference) to find a significant beneficial effect of supplemental calcium on colon/rectal cancer risk. Of the six prospectively designed observational studies, four reported some type of significant association for calcium supplements and the risk reduction of colon/rectal cancer (Flood et al., 2005; Wu et al., 2002; Sellers et al., 1998; McCullough et al., 2003), while two studies reported no association (Martinez et al., 2002; Hyman et al., 1998). The studies that reported a protective association for supplemental calcium were the cohorts that represented the largest number of subjects, contained both genders, and a broad age range of subjects. The effect of calcium on decreased colon/rectal cancer risk was modest and the effect did not seem to increase after a threshold of calcium intake was achieved (Wu et al., 2002) thereby suggesting that larger study populations are needed to find a modest reduction in risk. Of the four case-control studies, three studies reported no association between calcium intake and colon/rectal cancer (Marcas et al., 1998; Neugut et al., 1996; White et al., 1997) and one study reported a protective association between calcium and colon/rectal cancer risk (Whelan et al., 1999). Based on the above evidence, FDA concludes that there is a low level of comfort that a relationship exists between supplemental calcium intake and colon/rectal cancer.[22]

Breast Cancer

As discussed in Section II of this letter, there were no intervention studies on calcium intake and risk of breast cancer. There was one prospective cohort study that evaluated supplemental calcium intake and breast cancer risk and this study reported no association (Shin et al., 2002). Based on the above, FDA concludes that there is no credible evidence supporting a relationship between supplemental calcium intake and breast cancer.

Prostate Cancer

As discussed in section II of this letter, one prospective cohort l study evaluated the relationship between supplemental calcium intake and risk of prostate cancer (Giovannucci et al., 1998). This study reported that high consumption of calcium supplements and a low intake of dietary calcium increased the risk of developing metastatic prostate cancer. In addition, two case control studies (Kristal et al., 1999; Kristal et al., 2002) reported no significant association between supplemental calcium and reduced risk of prostate cancer. Based on the above, FDA concludes that there is no credible evidence supporting a relationship between supplemental calcium intake and prostate cancer.

Recurrent Colon/Rectal Polyps

As discussed in Section II of this letter, one intervention study reported a significant reduction in recurrent colon/rectal polyps after supplementation with 1.2 g/day of calcium (Baron et al., 1999). Another intervention study showed no significant benefit with calcium supplementation (Bonithon-Kopp et al., 2000). Baron et al. (1999) included more subjects and had a longer follow-up time which provided the study with more power (e.g., ability to detect a difference) to find a significant effect of calcium supplementation. Neither of the two prospective cohorts reported an association between supplemental calcium and colon/rectal polyp recurrence (Martinez et al., 2002; Hyman et al., 1998). One case-control study reported no association

between calcium supplements and polyp occurrence (Neugut et al., 1996), whereas another case-control study reported that supplemental calcium intake was associated with a reduced risk of polyp recurrence (Whelan et al., 1999). Based on the above, FDA concludes that there is a very low level of comfort that a relationship exists between supplemental calcium intake and recurrent colon/rectal polyps.[23]

IV. Other Enforcement Discretion Factors

Dietary supplements bearing the qualified health claim about calcium and reduced risk of colon/rectal cancer or colon/rectal polyps for which FDA intends to consider the exercise of its enforcement discretion must meet all applicable statutory and regulatory requirements under the Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. For example, such supplements must be labeled consistent with 21 CFR 101.36(b)(3). Dietary supplements also must not pose an unreasonable risk of illness or injury to the consumer or contain substances that may render the product injurious to health, or be otherwise adulterated or misbranded. In addition, FDA intends to consider the following factors in its exercise of enforcement discretion for qualified health claims about calcium and reduced risk of colon/rectal cancer or calcium and reduced risk of colon/rectal polyps.

A. Qualifying Level of Calcium

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for "high" has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (see 21 CFR 101.14(d)(2)(vii)).

A "high" definition is established for calcium; therefore, FDA intends to consider in the exercise of its enforcement discretion for dietary supplements bearing a qualified health claim about calcium and reduced risk of colon/rectal cancer or colon/rectal polyps described in Section VI when the dietary supplement contains calcium at a level that meets or exceeds the requirement for a "high" level of calcium as defined in 21 CFR 101.54(b) (i.e., 200 mg or more per RACC under the current regulation).

B. Assimilability of Calcium, Disintegration and Dissolution of Dietary Supplements

FDA intends to consider, as a factor in the exercise of its enforcement discretion for dietary supplements bearing a qualified health claim about calcium and colon/rectal cancer or colon/rectal polyps that the calcium content of dietary supplements is assimilable (i.e., bioavailable) (21 CFR 101.72(c)(ii)(B). Also, FDA intends to consider, as a factor in the exercise of its enforcement discretion that dietary supplements bearing such qualified health claims meet the United States Pharmacopeia (U.S.P.) standards for disintegration and dissolution applicable to their component calcium salts. For dietary supplements for which no U.S.P. standards exist, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that the dietary supplements exhibit appropriate assimilability under the conditions

of use stated on the product label (21 CFR 101.72(c)(ii)(C).

V. Agency's Consideration of Disclaimers or Qualifying Language

We considered but rejected use of a disclaimer or qualifying language to accompany the proposed claims for calcium and a reduced risk of breast cancer and prostate cancer. We concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances, where there is no credible evidence to support the claims. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the message conveyed by the unsubstantiated claim. See, e.g., *In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff'd*, 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co., 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."); *Pearson v. Shalala*, 164 F.3d 650, 659 (D.C. Cir 1999) (the court stated that, where the weight of evidence was against the claim, FDA could rationally conclude that the disclaimer "The FDA has determined that no evidence supports this claim" would not cure the misleadingness of a claim). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. Resort Car Rental System, Inc. v. FTC, 518 F.2d 962, 964 (9th Cir.) (per curiam) (upholding FTC order to excise "Dollar a Day" trade name as deceptive because "by its nature [it] has decisive connotation for which qualifying language would result in contradiction in terms."), cert denied, 423 U.S. 827 (1975); Continental Wax Corp. v. FTC, 330 F.2d 475, 480 (2d Cir. 1964) (same); Pasadena Research Labs v. United States, 169 F.2d 375 (9th Cir. 1948) (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g.*, United States v. Millpax, Inc., 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that "no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.*, 855 F. Supp. 534, 543 (D.R.I.) ("The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds*, 862 F. Supp. 717 (1994).

VI. Conclusions

Based on FDA's consideration of the scientific evidence and other information submitted with your petition, and other pertinent scientific evidence and information, FDA concludes that there is no credible evidence to support qualified health claims about calcium and breast cancer or calcium and prostate cancer. Thus, FDA is denying these claims. However, FDA concludes that there is sufficient evidence for qualified health claims about calcium and colon/rectal cancer and calcium and colon/rectal polyps, provided that the qualified claims are appropriately worded so as to not mislead consumers. Thus, FDA intends to consider exercising enforcement discretion for the following qualified health claims for dietary supplements:

1. "Some evidence suggests that calcium supplements may reduce the risk of colon/rectal cancer, however, FDA has determined that this evidence is limited and not conclusive."
2. "Very limited and preliminary evidence suggests that calcium supplements may reduce the risk of colon/rectal polyps. FDA concludes that there is little scientific evidence to support this claim."

FDA intends to consider exercising enforcement discretion for the above qualified health claims for dietary supplements when all other factors for enforcement discretion identified in Section IV of this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement, that will support a qualified health claim for those claims that were denied, that will no longer support the use of the above qualified health claim, or that raises safety concerns about the substance that is the subject of the claims.

Sincerely,

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Appendix 1

Please See Docket # 2004Q-0097 for each study and full citation.

Intervention studies that used people diagnosed with cancer

Thomas et al., 1993
Duris et al., 1996**

Intervention Studies that used a non-recognized surrogate endpoint of cancer

Alberts et al., 1996	Kleibeuker et al., 1993 Lans et al.,
Alberts et al.,1997	1991
Alder et al., 1993	Lapre et al., 1993
Armitage et al, 1995	Lipkin et al., 1985
Atillasoy et al., 1995	Lipkin et al., 1989
Baron et al., 1995	Love et al., 1990
Barsoum et al., 1992	Lupton et al., 1996

Bostwick et al., 1993*
Bostwick et al., 1995
Cascinu et al., 2000
Cats et al., 1995
Cats et al., 1993
Glinghammar et al., 1997
Gorkom et al., 2002
Gorkom et al., 2002
Govers et al., 1996
Gregoire et al., 1989
Holt et al., 2002
Hofstad et al., 1998
Holt et al., 2001**
O'Sullivan et al., 1993
Rozen et al., 1989
Rozen et al., 2000
Steinbach et al., 1994**
Wargovich et al., 1992
Weisgerber et al., 1996
Welberg et al, 1993
Welberg et al., 1994
Van Der Meer et al., 1990
Karagas et al., 1998**
Sandeler et al., 2000

Intervention studies that did not use/measure calcium or calcium was used in combination with another intervention.

Biasco et al., 1997
Hofstad et al., 1998
Hofstad et al., 1998
Holt et al., 2001**
Karagas et al., 1998**
Steinbach et al., 1994**
Suzuki et al., 1992

Reanalysis/Republication of an intervention study already used to evaluate the claim

Almendingen et. al., 2002
Grau et al., 2003
Baron et al., 1999

No statistical analysis

Duris et al., 1996**

Observational studies that estimated calcium intake only from dietary sources or water intake

Almedingen et al., 1995
Arbman et al., 1991
Benito et al., 1991
Benito et al., 1993
Boutron et al., 1996
Bostwick et al., 1993
Faivre et al., 1997
Ferraroni et al., 1994*
Freudenheim et al., 1990
Gaard et al, 1996

Geltner-Allinger et al., 1991
Ghadirian et al., 1997
Graham et al., 1988
Heilbrun et al., 1986
Jarvinen et al., 2001
Jie et al., 19
Kampman et al., 1994*
Kampman et al., 1994b
Kampman et al., 1994c
Kato et al., 1997
Katschinski et al., 2001
Kearney et al., 1996*
Kune et al, 1987
La Vecchia et al, 1997
Lee et al., 1989
Levi et al., 2000
Levine et al., 2001
Ma et al, 2001
Macquart-Moulin et al., 1986
Macquart-Moulin et al., 1987
Malilia et al, 1998
Martinez et al., 1996a
Martinez et al., 1996b
Martinez et al., 1997
Meyer et al., 1993
Morgan et al., 1995
Morimoto et al., 2002
Mower et al., 1979
Nakaji et al., 2003
Negri et al., 1990
Peters et al., 1992
Peters et al., 2001
Pietinen et al., 1999
Pritchard et al., 1996
Satie-About et al., 2003
Slattery et al., 1994
Slattery et al., 1999
Slattery et al., 2002
Slattery et al., 1988
Slattery et al., 1997
Slob et al., 1993
Stemmermann et al., 1990
Terry et al., 2002
Turjman et al., 1984
Tseng et al., 1996
Whittemore et al., 1990
Willet et al., 1990
Wu et al., 1987
Yang et al., 1998a

Yang et al., 1998b
Yang et al., 1999
Zaridze et al., 1993
Zheng et al., 1998

Observational studies on breast cancer that estimated calcium intake only from dietary sources

Boyapati et al., 2003
Graham et al., 1991
Katsouyanni et al., 1988
Kneckt et al., 1996
Negri et al., 1996
Van T' Veer et al., 1991
Zaridze et al., 1991

Observational studies on prostate cancer that estimated calcium intake only from dietary sources

Berndt et al, 2002
Chan et al., 2001
Chan et al., 2000
Chan et al., 1998
Hayes et al., 1999
Ohno et al., 1988
Schuurman et al., 1999
Tavini et al., 1999
Tzonou et al., 1999
Vlajinac et al, 1997

* Study (exact same publication) was submitted twice in the petition

** Study is listed twice in the appendix.

Notes

[1] "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003). [http://www.cfsan.fda.gov/~dms/nutrf-e.html]

[2] See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir 2004) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S.Ct. 310 (2004).

[3] See guidance entitled "Interim Evidence-based Ranking System for Scientific Data," July 10, 2003. [http://www.cfsan.fda.gov/~dms/hclmgui4.html]

[4] For brevity, "disease " will be used as shorthand for "disease or health-related condition " in the rest of the section.

[5] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See Guidance entitled "Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (December 22, 1999). [http://www.cfsan.fda.gov/~dms/ssaguide.html]

[6] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[7] Review articles summarize the findings of individual studies.

[8] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

[9] See *supra*, note 3.

[10] Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990) and Ioannidis JPA. Contradicted and initially stronger effects in highly cited clinical research. JAMA, 294: 218-228, 2005.

[11]Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300); See also Systems to rate the scientific evidence, Agency for Healthcare Research and Quality http://www.ahrq.gov/clinic/epcsums/strengthsum.htm#Contents, defining "consistency " as "the extent to which similar findings are reported using similar and different study designs."

[12] See *supra*, note 3.

[13] http://www.nci.nih.gov/cancertopics/commoncancers

[14] Calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate.

[15] See *supra*, note 2.

[16] Relative risk is expressed as the ratio of the risk (incidence) in exposed individuals to that in unexposed individuals (Epidemiology Beyond the Basics, page 93, Aspen Publishers, 2000).

It is calculated in prospective studies by measuring exposure (e.g. calcium supplements) in subjects with and without disease (e.g. specific type of cancer). An adjusted relative risk controls for potential confounders. Confidence intervals provide a statistical analysis (p value) of relative risk. 95% Confidence intervals (CI) that include 1.0 are not statistically significant.

[17] In a cohort study, a group of healthy people or cohort is identified and followed up for a certain time period to ascertain the occurrence of disease and or health related events. (Epidemiology Beyond the Basics, page 24, Aspen Publishers, 2000).

[18] In a case-control study, a group of cases are identified as the individuals in whom the disease of interest was diagnosed during a given year and controls are selected from individuals who do not have the disease in the same time period (Epidemiology Beyond the Basics, page 29 Aspen Publishers, 2000).

[19] Odds ratio is calculated in case control studies by measuring disease (e.g. cancer) development in subjects based on exposure (e.g. calcium). Confidence intervals provide a statistical analysis (p value) of the odds ratio. 95% Confidence intervals that include 1.0 are not statistically significant.

[20] See *supra*, note 10.

[21] See *supra*, note 11.

[22] See *supra*, note 3.

[23] See *supra*, note 3.